WO 02/24198 PCT/US01/29534
(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 March 2002 (28.03.2002)

PCT

(10) International Publication Number
WO 02/24198 A1

(51) International Patent Classification[7]: A61K 31/403, 31/138, A61P 11/06

(21) International Application Number: PCT/US01/29534

(22) International Filing Date:
20 September 2001 (20.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/234,257 21 September 2000 (21.09.2000) US

(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF HOUSTON** [US/US]; 316 E Cullen Building, Houston, TX 77204-2015 (US).

(71) Applicant and
(72) Inventor: **BOND, Richard, Agustin** [US/US]; University of Houston, 4800 Calhoun, Houston, TX 77204 (US).

(74) Agents: **LEVY, David, J.** et al.; GlaxoSmithKline, Five Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709-3398 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/24198 A1

(54) Title: NOVEL THERAPY

(57) Abstract: Use of a β-antagonist in the manufacture of a medicament for the treatment or prophylaxis of allergic or inflammatory disorders and method of treament of allergic or inflammatory disorders in a human or animal subject which comprises administering to said human or animal subject an effective amount of a β-antagonist.

NOVEL BETA-ANTAGONIST THERAPY

The present invention relates to the novel use of β-adrenoceptor antagonists (β-antagonists/ β-blockers) for the treatment of allergic and inflammatory disorders and the prophylactic treatment thereof.

Allergic and inflammatory disorders include: skin disorders such as dermatitis, eczema, allergen induced rashes; diseases of the upper airways such as asthma, chronic bronchitis, emphysema, Chronic Obstructive Pulmonary Disease (COPD) and rhinitis.

Asthma affects an estimated 17 million Americans. In recent decades the rate of morbidity and mortality of asthma have increased. Persons suffering from asthma are often sensitive to allergens, such as household dust, animal hairs and pollen (allergic asthma). However intrinsic asthma may be triggered in a patient by, for example, emotional distress or panic. Asthma attacks are characterised by shortness of breath, caused by contraction of the smaller bronchi and bronchioles, chest tightness, coughing and wheezing. The attacks can be mild, intermediate or severe.

Chronic bronchitis is an inflammation of the bronchial tubes. This may be due to exposure to environmental irritants, which results in inflammatory changes in the airways.

Emphysema results from chronic, progressive destruction of the alveolar structure. This may be due to exposure to environmental irritants but is often associated with cigarette smoking.

COPD is also a degenerative disease where the bronchi and bronchioles lose their elasticity either due to the ageing process or by exposure to environmental irritants.

The diseases above often have similar characteristics including shortness of breath, coughing, wheezing, mucus and fluid build up.

Traditionally allergic and inflammatory respiratory disorders have been treated by a bronchodilator such as a β-agonist, for example, albuterol (also known as Ventolin™) or salmeterol, and/or an anti-inflammatory steroid, for example, budesonide or fluticasone propionate, often by inhalation therapy. In theory the former gives rapid symptomatic relief through bronchodilation and the latter treats the underlying inflammation and thereby reduces the frequency of occurence and severity of attacks.

The key role of β-agonists as bronchodilators in the treatment of asthma has been assumed for years and is currently confirmed through the treatment guidelines, for example, those of the British Thoracic Society on the management of chronic asthma in adults (UK) and the National Heart, Lung and Blood Institute Guidelines on the Diagnosis and Management of Asthma (US).

It is well established that β-blocking agents, such as those that are frequently used in the treatment of cardiovascular conditions are definitely contraindication for asthmatic patients. In "Practical Management of Asthma" (second edition) by Tim Clark and John Rees (published by Martin Dunitz) (1996) it is stated:

> "These (β-blockers) often produce adverse effects when given to asthmatics. Treatment with beta blockers can also bring to light previously undiagnosed asthma. Fatal bronchoconstriction has been produced by a single dose of beta blockers.....It is best to avoid all beta blockers in asthmatics."

In summary, such agents would be expected to cause bronchoconstriction and negate the effect of the bronchodilatory therapy.

β-antagonists are currently used as antihypertensives and antianginal agents. Some have additional antiarrhythmic and/or antiglaucoma properties.

Surprisingly, however, the inventor has found that β-antagonists may indeed be useful in the treatment of and prophylaxis of allergic and inflammatory disorders, especially respiratory diseases.

The expression β-antagonist when used in this specification will be understood to refer to substances which act as antagonists and/or inverse agonists of β-adrenoceptors.

According to one aspect of the invention, there is provided the use of a β-antagonist in the manufacture of a medicament for the treatment or prophylaxis of allergic or inflammatory disorders, especially respiratory disorders such as asthma or COPD.

According to another aspect, there is provided a method of treatment of allergic or inflammatory disorders, especially respiratory disorders such as athma or COPD, in a human or animal subject which comprises administering to said human or animal subject an effective amount of a β-antagonist.

According to a further aspect there is provided a method of treatment of histadine mediated allergic or inflammatory disorders in a human or animal subject which

comprises administering to said human or animal subject an effective amount of a β-antagonist.

The β-antagonist may have β_1-antagonist activity and/or β_2-antagonist activity. Preferably the β-antagonist will have β_2-antagonist activity, more preferably selective β_2-antagonist activity over β_1-antagonist activity.

Whilst not wishing to be bound by theory, the use of a β-antagonist in the treatment or prophylaxis of allergic or inflammatory disorders is supported in part by the hypothesis of paradoxical pharmacology related to the fact that the acute and chronic effects of drug therapy can often be opposite in nature. This is especially true for receptor mediated events. The theory, in general, suggests that by increasing the stress and exacerbating the symptoms of the disease in some instances the body is forced in the longer term to compensate for this and provide mechanisms for improving the patient's condition. Thus the body's own healing mechanisms are stimulated rather than substituted.

β-antagonists include: acebutolol (e.g. as hydrochloride [HCl]); alprenolol (e.g. as HCl); amosulalo (e.g. as HCl); arnolol; arotinolol (e.g. as HCl); atenolol; befunolol (e.g. as HCl); betaxolol (e.g. as HCl); bevantolol (e.g. HCl); bisoprolol (e.g. as hemifumarate); bopindolol (e.g. as maleate or malonate); brefonalol; broxaterol; bucumolol (e.g. as HCl); bufetolol (e.g. as HCl); bufuralol (e.g. as HCl); bunitrolol (e.g. as HCl); bupranolol (e.g. as HCl); butidrine (e.g. as HCl); butofilolol (e.g. as maleate); carazolol; carteolol (e.g. as HCl); carvedilol; celiprolol (e.g. as HCl); cetamolol (e.g. as HCl); cloranolol (e.g. as HCl); dilevalol (e.g. as HCl); epanolol; esmolol (e.g. as HCl); falintolol; idropranolol; indenolol (e.g. as HCl); labetalol (e.g. as HCl); landiolol; levobunolol (e.g. as HCl); mepindolol; metipranolol (e.g. as HCl); metoprolol (e.g. as fumarate, succinate or tartrate); moprolol (e.g. as HCl); nadolol; nadoxolol (e.g. as HCl); nebivalol; nifenalol (e.g. as HCl); nipradilol; oxprenolol (e.g. as HCl); pacrinolol; pafenolol; pargolol; penbutolol (e.g. as sulphate); penirolol; pindolol; pirepolol; practolol; procinolol; pronethalol (e.g. as HCl); propranolol (e.g. as HCl); ridazolol; soquinolol; sotalol (e.g. as HCl); spirendolol; sulfinalol (e.g. as HCl); talinolol; teoprolol; tertatolol (e.g. as HCl); tienoxolol; tilisolol (e.g. as HCl); timolol (e.g. as maleate); toliprolol (e.g. as HCl), xibenolol (e.g. as HCl) and ICI 118, 551 and salts and solvates thereof.

Pharmaceutically acceptable salts include: acid salts such as, hydrochloride, sulphate, fumarate, maleate, malonate, succinate, and tartrate, alkali metal salts such as sodium or potassium. Examples of solvates include hydrates.

Especially preferred for use, according to the invention, are alprenolol, carvedilol, cetamolol, metoprolol and atenolol, particularly alprenolol, carvedilol and atenolol, more particularly alprenolol and carvedilol, especially carvedilol or a salt or solvate of any one thereof. ICI 118, 551 is also of interest.

Work to confirm this hypothesis has been carried out by the inventor with allergen sensitised mice (details of which are contained in the Example 1). This work concluded that chronic treatment with the β-adrenoceptor antagonist, alprenolol and with the β-adrenoceptor antagonist/inverse agonist, carvedilol significantly reduced the contractile response to methacholine in allergen sensitised and challenged mice. The β-adrenoceptor antagonist ICI 118, 551 also reduced the contractile response to methacholine in allergen sensitised and challenged mice. The data is consistent with the hypothesis that β-blockers may be useful in the treatment of respiratory diseases such as asthma and other chronic obstructive pulmonary diseases.

Additional work by the inventor with ovalbumin sensitized guinea pigs (details of which are contained in Example 2) further supports the theory that β-blockers may be useful in the treatment of histamine mediated allergic reactions.

Use of the β-antagonist in the treatment or prophylaxis of asthma and COPD form a preferred aspect of this invention.

The β-antagonist may be used in conjunction with one or more pharmaceutical excipients.

Thus the β-antagonist may be formulated for oral, buccal, parenteral, transdermal, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

Thus there is also provided a pharmaceutical formulation for use in the treatment or prophylaxis of allergic and inflammatory respiratory disorders which comprises a β-antagonist in admixture with one or more pharmaceutical acceptable diluents or carriers.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example,

magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or toxicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a

vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2-tetrafluoroethane, carbon dioxide or other suitable gas.

Capsules, of for example, gelatin, and cartridges, for use in an inhaler or insufflator, may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

The compound of the invention may conveniently be administered in amounts of, for example: carvedilol 0.01 to 50mg suitably 0.05 to 25mg orally one or more times a day; atenolol up to 100mg per day and alprenolol 5 to 300mg per day. The dosing regime may start with a low dose which is gradually increased to improve the patient's tolerance of the therapy.

The precise dose will of course depend on the age and condition of the patient, the particular route of administration chosen, and the disease being treated. The compound is preferably administered orally.

The β-antagonist may, if desired, be administered together with one or more other therapeutic agents and formulated with one or more excipients for administration by any convenient route in a conventional manner.

According to the invention there is also provided use of a β-antagonist in the preparation of a pharmaceutical formulation for use in the treatment or prophylaxis of allergic or inflammatory disorders, especially respiratory disorders, particularly asthma or COPD.

Example 1

Male 6 week old Balb/cJ mice were obtained from the breeding colony of the Jackson Laboratory, Bar Harbor, Maine. The mice were housed in filtered cages and provided food and water *ad libitum*. Active allergen sensitisation was performed by injections with 10 µg ovalbumin (grade II, Sigma Chemical Company, St. Louis, MO.) in 0.5 mL pyrogen free saline intra-peritoneally on alternate days for 14 days. Ten days following the last sensitisation injection, the mice were treated with either vehicle (DMSO) or three $ß_2$-adrenoceptor ligands. Drug treatments were performed using Alzet (model #2002, ALZA Corp., Palo Alto, CA.) osmotic minipumps inserted subcutaneously on the dorsal side of the mouse for infusion. The doses were chosen to provide >90% receptor occupancy based on prior experiments and were as follows: alprenolol, 1.2 mg/kg/h; carvedilol, 0.4 mg/kg/h; and ICI-118, 551, 0.7 mg/kg/h. The mice were briefly anaesthetised via inhalation with halothane and a small incision was made on their back for insertion of the pump. The incision was closed using surgical staples and the mice were returned to their cages. Drug treatment lasted 19 days, on day 18 mice were exposed to ovalbumin (2 mg/ml) aerosol for 5 min. The aerosol was generated with a nebulizer (CIS-US, Inc., #CA 209) connected to a plexiglass exposure chamber. Aerosol was given either alone or in groups of a maximum of four mice. Following 24 hours after inhaling the aerosolised protein, the mice were killed (1 to 2 hrs following the end of pump infusion). The trachea was isolated, dissected free of connective tissue and suspended for recording the tension developed by a contractile agent, methacholine, in an organ bath. The lungs and heart were isolated and immediately frozen in liquid nitrogen and stored at –80° C until assay for G protein levels. A concentration response curve to methacholine was performed in control (no allergen-sensitized, no drug treatment), allergen-sensitized with no drug treatment, and allergen-sensitized drug treated mice.

Mice were anaesthetised via 0.2 mL injection of Nembutal (10 mg/ml). An incision was made at the bottom of the sternum proceeding laterally to the axillae. The skin was retracted from the chest plate and the chest plate was removed by cutting through the rib cage. The trachea was located, removed and transferred to a petri dish containing Krebs' bicarbonate solution (118.1 mmol/L NaCl; 25 mmol/L $NaHCO_3$; 11.1 mmol/L glucose; 4.7 mmole/l KCl; 0.5 mmol/L $MgCl_2 \cdot 6H_2O$; 1.0 $NaH_2PO_4 \cdot H_2O$; 2.5 mmol/l $CaCl_2 \cdot 2H_2O$; pH 7.4) being constantly gassed with a mixture of 95% O_2 and 5% CO_2. There all connective tissue was removed from the trachea and thereafter, was

mounted in an organ bath (13 mL) filled with Krebs' solution. The organ bath was constantly gassed with a mixture of 95% O_2 and 5% CO_2 and a temperature of 32° C was maintained. Changes in tracheal muscle contraction were measured using an isometric transducer (Harvard Apparatus, Inc., Holliston, MA) connected to a 4-channel pen recorder (Hewlett-Packard Co., Wilmington, DE). After a stabilizaiton period (45 min) at a basal tension (500-1000 mg), the tracheae were bathed with 1 mM acetylcholine, washed with Krebs' solution 6 times with an interval of 3 min. before cumulative concentration response curves were made with methacholine. The concentration response curves started with a concentration of 1×10^{-9} M and ended with a concentration of 1×10^{-3} M. Results were expressed as per cent change in baseline tension or in absolute mgs of developed tension.

Figure1: Different tracheal contractile responses to methacholine in sensitized and challenged (□, n=6) or control (●, n=10) mice. Mice were injected with ovalbumin for 14 days every other day, and were challenged by inhaling ovalbumin aerosol for 5 min. 24 hours after exposure to ovalbumin aerosol, the mice were killed and the trachea isolated for functional studies. Baseline tension was set to 500-1000mg in each preparation and dose response curves to methacholine were performed (10nM–100μM). Data are expressed as mean +/- S.E.M (standard error of the mean).

Figure 2: Different tracheal contractile responses to methacholine in sensitized and challenged (□, n=6) or control (●, n=10) mice compared to sensitized, challenged and drug treated mice (○ carvedilol, n=7; ▲ ICI 118,551, n=10; ■ alprenolol, n=8). Mice were injected with ovalbumin for 14 days every other day. Ten days later osmotic minipumps were inserted subcutaneously on the dorsal side of the mice and drug treatment started for 19 days. On day 18 the mice were challenged by inhaling ovalbumin aerosol for 5 min. 24 h after exposure to ovalbumin aerosol, the mice were killed and the trachea isolated for functional studies. Baseline tension was set to 500-1000mg in each preparation and dose response curves to methacholine were performed (10nM–100μM). Data are expressed as mean +/- S.E.M.

Data Analysis of Figure 1 and Figure 2

Unless stated otherwise, data are expressed as mean ± S.E.M. ANOVA was applied to compare more than two groups (Bonferroni or Fischer post-hoc test) $p < 0.05$ was considered significant. Statistical analyses were carried out using StatView, version 5.0 (SAS Institute Inc., Cary, NC)

Figure 1 shows tracheal contractile responses to methacholine in control mice versus the allergen sensitised and challenged mice. The contractile response was enhanced in

the allergen sensitised and challenged group. Figure 2 shows that chronic treatment (19 days) with the β-adrenoceptor antagonist, alprenolol significantly reduced the contractile response to methacholine in allergen sensitised and challenged mice.

Figure 2 also shows that chronic treatment (19 days) with the β-adrenoceptor antagonist/inverse agonist, carvedilol, also significantly reduced the contractile response to methacholine in the allergen sensitized and challenged mice.

After chronic treatment (19 days) with the research tool ICI 118 551 the contractile response to methacholine in allergen sensitized and challenged mice was reduced.

Example 2

Male guinea pigs (Dunkin-Hartley, *c.* 200 g) were obtained from the breeding colony of Harlan, Dublin, Virginia. The guinea pigs were housed in filtered cages and provided food and water *ad libitum*. Ovalbumin (10 µg/mL, grade II, Sigma Chemical Company, St. Louis, MO.) was mixed with aluminium hydroxide (10 mg/mL, Sigma Chemical Company, St. Louis, MO.) in 1 mL pyrogen free saline and injected subcutaneously. Identical injections of ovalbumin were made 15 and 21 days later. On the second day following the initial sensitisation, the guinea pigs were given control chow (C in figure 3) or chow treated with the β-adrenoceptor antagonist/inverse agonist, carvedilol (2400 ppm, Harlan Teklad, Madison, WI) (C 1 in figure 3). The responsivity of guinea pigs that had been sensitized to the antigen ovalbumin was determined by two intracutaneous injections of ovalbumin (10 µg per site) in the flank skin of the hind limb on the 28th day following the initial sensitisation. The responsivity of four animals that had been returned to control chow for 2 to 4 days following 28 days of carvedilol chow was also determined (C 2 in figure 3). A positive reaction consisted of one or two overt skin responses (flare and wheal) greater than 1cm in diameter.

Figure 3 shows the number of animals with at least 1 positive reaction site in three animals groups. Chronic treatment with carvedilol eliminated the inflammatory flare and wheal responses, attributed to histamine, in 100% of guinea pigs tested (4 out of 4 animals). In the control group 88% of guinea pigs tested (29 out of 30 animals) exhibited inflammatory flare and wheal responses. Carvedilol treated guinea pigs that were returned to control chow 2 to 4 days before responsivity testing, showed the inflammatory flare and wheal responses in 100% of animals tested (4 out of 4 animals).

In figure 3: C represents the control (allergen sensitized animals no drug treatment), C 1 represents allergen sensitized animals treated with carvedilol and C 2 represents allergen-sensitized animals treated with carvedilol upto 2-4 days before testing.

A Brief Description of The Figures

Figure 1 shows tracheal contractile responses to methacholine in control mice versus the allergen sensitized and challenged mice.

Figure 2 shows tracheal contractile responses to methacholine in sensitize and challenged mice, some which were: untreated (the control), treated with carvedilol, treated with ICI 118, 55, treated with alprenolol.

Figure 3 shows shows the percentage of animals with at least 1 positive visible reaction site to ovalbumin in sensitized and challenged guinea pigs, some which were: untreated (the control), treated with carvedilol, treated with carvedilol but untreated for 2-4 days before the test.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

Claims:

1. Use of a β-antagonist in the manufacture of a medicament for the treatment or prophylaxis of allergic or inflammatory disorders.

2. A method of treatment of allergic or inflammatory disorders in a human or animal subject which comprises administering to said human or animal subject an effective amount of a β-antagonist.

3. Use or a method of treatment as claimed in claim 1 or claim 2, wherein the inflammatory disorder is a respiratory disorder.

4. Use or a method of treatment as claimed in claim 3, wherein the respiratory disorder is asthma.

5. Use or a method of treatment as claimed in claim 3, wherein the respiratory disorder is COPD.

6. Use or a method of treatment as claimed in any one of claims 1 to 5, wherein the β-antagonist is carvedilol or a salt or solvate thereof.

7. Use or a method of treatment as claimed in any one of claims 1 to 5, wherein the β-antagonist is alprenolol or a salt or solvate thereof.

8. Use of a β-antagonist in the preparation of a pharmaceutical formulation for the treatment or prophylaxis of respiratory disorders.

9. A pharmaceutical formulation for use in the treatment or prophylaxis of allergic or inflammatory respiratory disorders which comprises a β-antagonist in admixture with one or more pharmaceutical acceptable diluents or carriers.

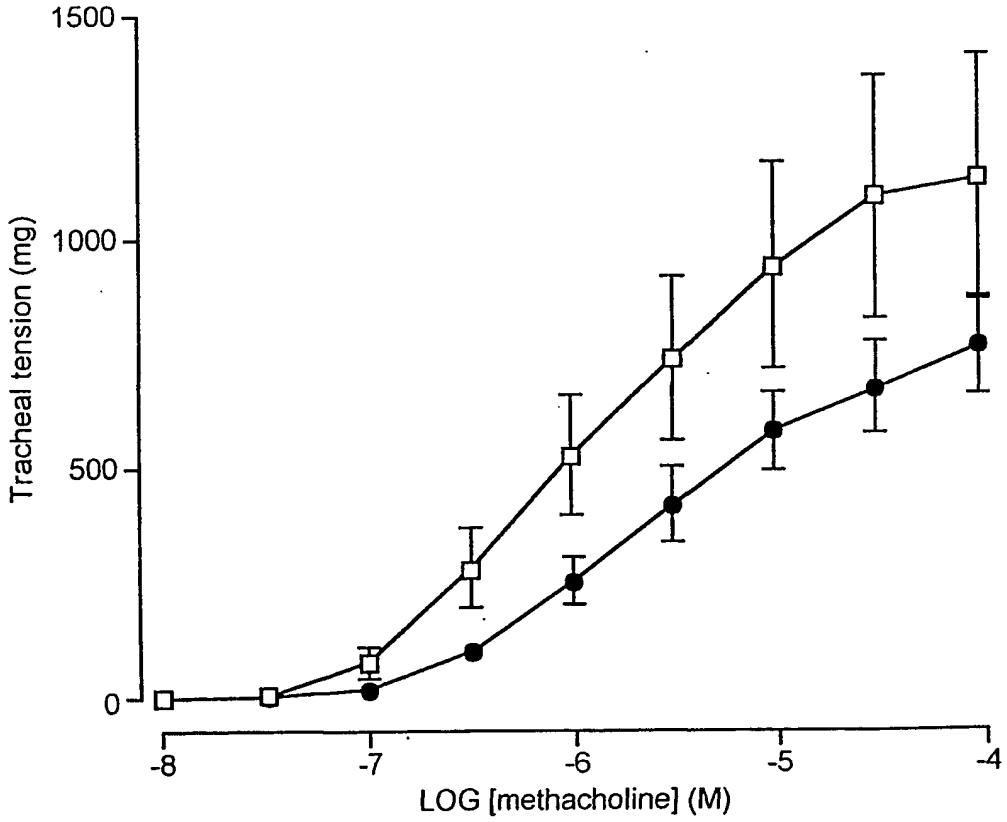
1500
1000
500
0
Tracheal tension (mg)
-8
-7
-6
-5
-4
LOG [methacholine] (M)

FIG. 1

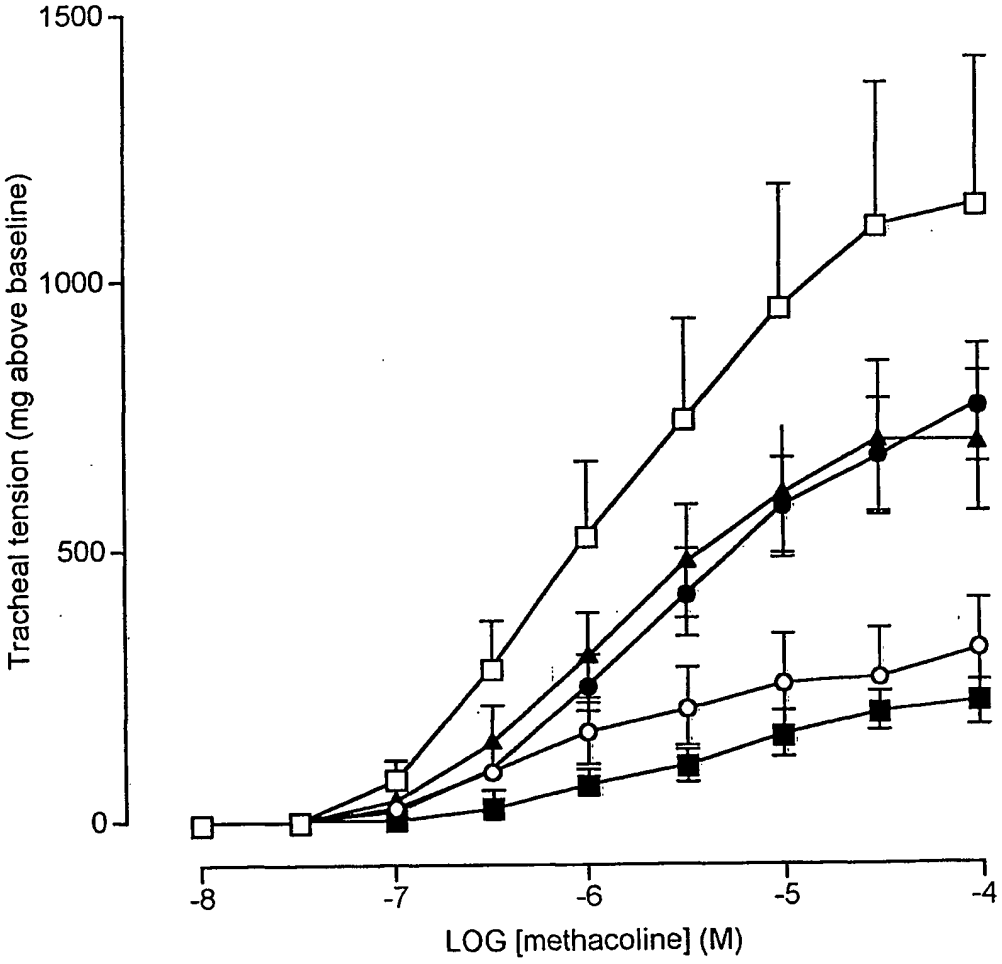
1500
1000
500
0
Tracheal tension (mg above baseline)
-8
-7
-6
-5
-4
LOG [methacoline] (M)

FIG. 2

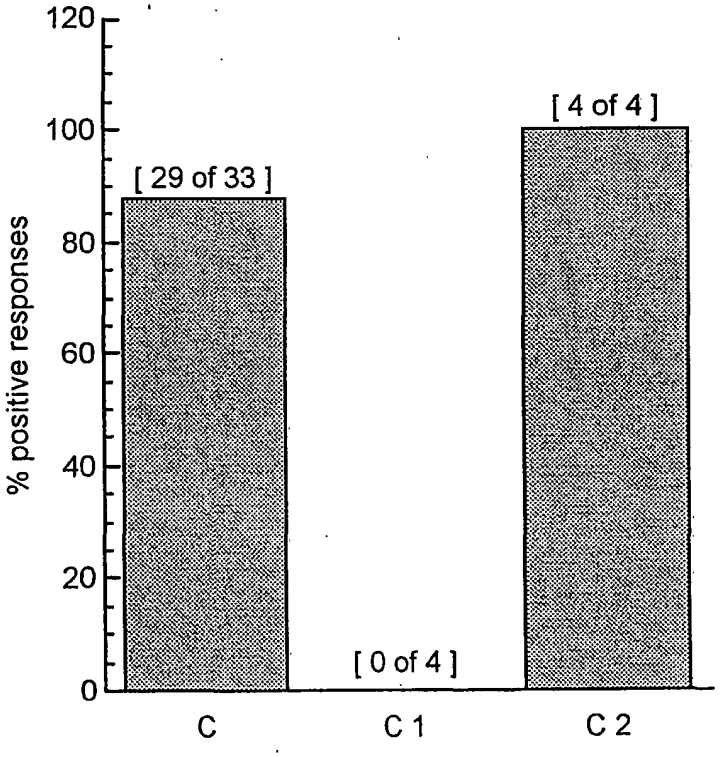
120
100
80
60
40
20
0
% positive responses
[29 of 33]
[0 of 4]
[4 of 4]
C
C 1
C 2

FIG. 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/29534

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/403 A61K31/138 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, PASCAL, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 908 387 A (LEVINE JON D ET AL) 13 March 1990 (1990-03-13) column 5, line 1; claim 1	1,3,8,9
Y		4,5
X	WO 98 38985 A (BOEHRINGER MANNHEIM GMBH ;MATSUMORI AKIRA (JP)) 11 September 1998 (1998-09-11) claim 2	1,6
X	US 5 116 867 A (KLEIN DAVID C ET AL) 26 May 1992 (1992-05-26) column 2, line 59 - line 68 column 3, line 11 - line 12	7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2002	25/02/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zimmer, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	O'BYRNE P M ET AL: "THE MANY FACES OF AIRWAY INFLAMMATION. ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE" AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, AMERICAN LUNG ASSOCIATION, NEW YORK, NY, US, vol. 159, no. 5, 1999, pages 541-566, XP000911062 ISSN: 1073-449X page 556, right-hand column, last paragraph	4,5
P,X	US 6 284 800 B1 (AHMED TAHIR ET AL) 4 September 2001 (2001-09-04) claims 1,2	1,3,4,6, 8,9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/29534

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4908387 A	13-03-1990	WO 8911851 A1	14-12-1989
WO 9838985 A	11-09-1998	JP 10251147 A	22-09-1998
		AU 6920398 A	22-09-1998
		WO 9838985 A2	11-09-1998
US 5116867 A	26-05-1992	AU 5967390 A	17-01-1991
		WO 9100259 A1	10-01-1991
US 6284800 B1	04-09-2001	US 2002013373 A1	31-01-2002